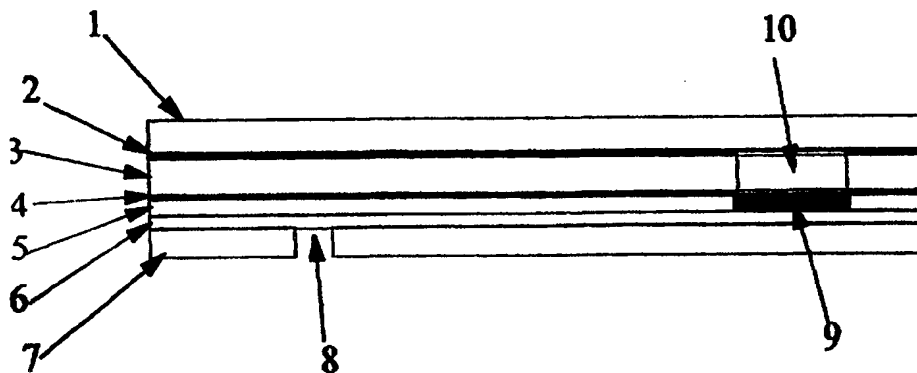




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/AU99/00152 <b>(22) International Filing Date:</b> 11 March 1999 (11.03.99)  <b>(30) Priority Data:</b> PP 2388                      12 March 1998 (12.03.98)                      AU  <b>(71) Applicant (for all designated States except US):</b> USF FILTRATION AND SEPARATIONS GROUP INC. [US/US]; 2118 Greenspring Drive, Timonium, MD 21093 (US).  <b>(72) Inventors; and</b> <b>(75) Inventors/Applicants (for US only):</b> HODGES, Alastair, McIndoe [AU/AU]; 15 Jasmine Court, Blackburn South, VIC 3130 (AU). BECK, Thomas, William [AU/AU]; 121 Keda Circuit, North Richmond, NSW 2754 (AU).  <b>(74) Agent:</b> BALDWIN SHELSTON WATERS; 60 Margaret Street, Sydney, NSW 2000 (AU).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>

**(54) Title:** HEATED ELECTROCHEMICAL CELL



**(57) Abstract**

The invention provides a method for determining the concentration of an analyte in a sample comprising the steps of heating the sample and measuring the concentration of the analyte or the concentration of a species representative thereof in the sample at a predetermined point on a reaction profile by means that are substantially independent of temperature. Also provided is an electrochemical cell comprising a spacer (3) pierced by an aperture which defines a cell wall, a first metal electrode (2) on one side of the spacer extending over one side of the aperture, a second metal electrode (4) on the other side of the spacer extending over the side of the aperture opposite the first electrode, means for admitting a sample to the cell volume defined between the electrodes and the cell wall, and means for heating a sample contained within the cell (10).

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## HEATED ELECTROCHEMICAL CELL

### TECHNICAL FIELD

5        This invention relates to a method and apparatus for measuring the concentration of an analyte in solution.

      The invention will be described with particular reference to the measurement of the concentration of glucose in blood but is not limited to that use and has general application for the measurement of analytes other than glucose and for solutions other  
10    than blood samples.

### BACKGROUND ART

      Persons who suffer from diabetes routinely check their blood glucose concentration and there is a need for simple, reliable and inexpensive means to facilitate such routine testing.

15        In a common method for conducting the tests, a blood sample is combined with an enzyme for example glucose dehydrogenase ("GDH"); the GDH oxidises glucose and in the process becomes reduced. An oxidising mediator for example ferricyanide is allowed to react with the reduced GDH returning the GDH to its initial form and producing ferrocyanide in the process. The concentration of ferrocyanide produced is  
20    then sensed for example electrochemically or spectroscopically to produce a signal which can be interpreted to give an estimate of the glucose concentration in the sample.

      In our co-pending applications PCT/AU96/00723 and PCT/AU96/00724 (the disclosures of which are incorporated herein by reference) there are described methods and apparatus suitable for electrochemically determining the concentration of glucose in  
25    blood by electrochemical measurement.

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A preferred method for accurately determining the concentration of an analyte is to react all the analyte present in the sample with reagents that produce a species that can be sensed. This requires that the reaction of the analyte go to completion.

For reaction of GDH with glucose to go to substantial completion typically  
5 requires several minutes. This is thought to be due to the time required for the glucose to diffuse out from glucose-containing cells of the blood. As this length of time is unacceptably long for the market, it is more usual to measure the glucose concentration over a shorter period, for example 20-30 seconds and accept a less accurate response or apply a factor to estimate the glucose concentration by kinetic extrapolation for example  
10 as outlined in co-pending application PCT/AU96/00723. This expedient shortens the time of the test but can lead to loss of precision of the result.

It is an object of the present invention to provide a method and apparatus which avoids or ameliorates the above-discussed deficiencies in the prior art.

#### DESCRIPTION OF THE INVENTION

15 According to one aspect the invention consists in a method for determining the concentration of an analyte in a sample comprising the steps of:

heating the sample in a disposable test cell; and

measuring the concentration of the analyte or the concentration of a species  
representative thereof in the sample at a predetermined point on a reaction profile by  
20 means that are substantially independent of temperature.

Those skilled in the art will understand the term "reaction profile" as used herein to mean the relationship of one reaction variable to another. Often, for example, the reaction profile illustrates the change of concentration of a species with respect to time.

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Such a profile can provide a skilled addressee with both qualitative and quantitative information, including information as to whether a reaction system has achieved a steady state.

Preferably, the predetermined point on the reaction profile is a steady state, and  
5 the species representative of the concentration of the analyte is a mediator, for instance an enzyme mediator.

In one embodiment of the invention the sample is heated by an exothermic reaction produced upon contact of the sample with a suitable reagent or reagents.

In a second embodiment of the invention the sample is heated electrically, for  
10 example by means of a current applied to resistive elements associated with the measuring means.

In a highly preferred embodiment the measuring means is an electrochemical cell of the kind described in co-pending applications PCT/AU96/00723 and PCT/AU96/00724 and the sample is heated by application of an alternating voltage  
15 signal between electrodes of the sensor.

According to a second aspect the invention consists in an electrochemical cell comprising a spacer pierced by an aperture which defines a cell wall, a first metal electrode on one side of the spacer extending over one side of the aperture, a second metal electrode on the other side of the spacer extending over the side of the aperture  
20 opposite the first electrode, means for admitting a sample to the cell volume defined between the electrodes and the cell wall, and means for heating a sample contained within the cell.

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## BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be more particularly described by way of example only with reference to the accompanying drawings wherein:

Figure 1 shows schematically a sensor strip according to the invention in a cross-section taken longitudinally through the midline of the sensor strip.

Figure 2 shows the results of tests conducted in accordance with one embodiment of the present invention for blood samples with varying haematocrits and glucose concentrations.

Figure 3 shows the results of tests conducted in accordance with another embodiment of the present invention for blood samples with varying haematocrits and glucose concentrations.

## BEST MODE FOR CARRYING OUT THE INVENTION

In preferred embodiments of the method of the invention, glucose concentration is measured using an electrochemical cell of the kind described in PCT/AU96/00723 and/or PCT/AU96/00724 (our co-pending applications). The method of measurement described in those applications utilises an algorithm which enables the value of the diffusion coefficient of the redox mediator to be calculated and the concentration of reduced mediator to be determined in a manner which is substantially independent of sample temperature. The method therein described is different from prior art methods which measure Cottrell current at known times after application of a potential. The present invention differs in that the sample is heated.

In a first embodiment of the present method the blood sample is heated prior to and/or during conduct of the electrochemical measurement by means of an exothermic

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reaction. In the first embodiment a reagent that liberates heat on contact with blood is contained within the sensor cell. Examples of such reagents are salts which give out heat when they dissolve such as aluminium chloride, lithium halide salts, lithium sulphate, magnesium halide salts and magnesium sulphate. Another class of reagents which would be suitable are those with two components which liberate heat upon mixing. These two components would be placed in separate locations in the sensor during fabrication, for example on coatings upon opposite internal cell walls and are deployed such that when a sample is introduced into the sensor at least one of the components dissolves and then comes into contact with the second component. Upon contact the two components react to liberate heat. The reagents used to generate the heat must not adversely effect the function of the other active elements in the sensor. For instance, they must not corrode the electrode materials, denature an enzyme if present, or adversely interact with any mediator that may be present. Upon introducing a sample of blood into the sensor heat is liberated and the temperature of the blood sample is raised. This facilitates reaction of the glucose with the GDH and since the measurement of ferrocyanide concentration is temperature independent an accurate assessment of glucose concentration can be made in a much shorter time than would otherwise be possible.

Less preferably, the heat generating reagent can be added after the sample is admitted to the cell.

Preferably the sample temperature is raised by from 5 to 15°C, for example from 20°C to 30°C or 35°C within a period of 2 to 10 seconds. The temperature peak is desirably reached within 2-5 seconds.

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A second embodiment of the invention employs a cell in which an electrically resistive element is incorporated. The sample may then be electrically heated by passing a current through the resistive element. For example, with reference to figure 1 there is shown an electrochemical sensor comprising a plastic substrate 1 bearing a first

5 electrode 2 (for example a sputtered layer of gold), a separator layer 3 having a circular aperture punched out which defines a cell volume 10 bounded on one cylindrical face by first electrode 2. The opposite face of cylindrical cell 10 is covered by a second electrode layer 4 (for example a sputter coating of palladium) which in this case is carried by a rubber or plastic layer 5. A metal foil layer 6 provides electrical contact to a

10 resistive bridge 9 formed in the rubber or plastic layer 5. An insulating layer 7 for example of plastic provides insulation against heat loss through the metal foil. An aperture 8 in layer 7 provides for electrical contact with metal foil layer 6. Resistive bridge 9 is formed for example from carbon particles impregnated into the rubber or plastic of layer 5 at a loading and of a geometry such as to give a suitable electrical

15 resistance between metal foil 6 and electrode layer 4. This method has the advantage of concentrating the heating effect adjacent the cell. Resistive heating elements may be fabricated by other means for example by coating an electrically conducting substrate with an electrically insulating layer which can be made partially conductive in particular regions if desired for example by exposure to particular chemicals and light.

20 When using a cell according to the second embodiment the sample is admitted to the cell, a potential is applied across the resistive element, and after the required amount of heat has been generated the potential across the resistive element is interrupted and after



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an optional wait time a potential is applied between the first electrode and second electrode to perform the electrochemical assay of the analyte.

Alternatively the potential across the resistive element can be maintained during the assay of the analyte at its initial level or at a lower level sufficient to substantially  
5 maintain the sample temperature at the desired level.

In another embodiment, the means for applying the potential to the resistive element is such that the current flowing through the resistive element is monitored and the potential automatically adjusted so as to maintain the required power output. This heats the sample in a reproducible fashion, even if the resistance of the resistive element  
10 varies from one sensor to the next. Furthermore, the power level required can be adjusted on the basis of the ambient temperature measured by a separate sensor. The leads to a more reproducible sample temperature being reached over a range of ambient temperature at which the sensor is being used.

In a third embodiment of the invention the sample is heated simply by applying an  
15 alternating voltage signal between the working and counter-electrodes of a sensor, for example, of the kind described in our co-pending applications. If this alternating voltage signal has a correct frequency and amplitude it will heat the sample while still allowing an accurate determination of the analyte to be subsequently made by the sensor. Because the voltage signal is alternating any reaction that occurs during one half voltage cycle is  
20 reversed during the second half of that cycle, resulting in no net change but in the dissipation of energy that will appear as heat in the sample. This is particularly applicable to sensors of the type disclosed in our abovementioned co-pending patent

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applications where any small changes that may occur in the cell are quickly removed after interruption of the alternating potential as the cell relaxes back to its initial stage.

When using cells such as described in our co-pending applications the sample volumes are very small and heating can be achieved with low energy input.

## 5   EXAMPLES OF HEATED STRIP EXPERIMENTS

### Example 1

Disposable test strips of the type described in PCT/AU96/00724 were heated by placing a metal bar, heated to 50°C, in contact with the sample receiving area of the strip. Whole blood samples were introduced into the sample receiving area of the strip  
10   and 13 seconds allowed for the glucose present in the sample to react with the sensor reagents. Current was then collected for ten seconds and analyzed according to the methods described in PCT/AU96/00723. The results of these tests for blood samples with haematocrits of 67.5%, 49.5% and 20% and glucose concentrations between 2.5 mM and 30 mM are shown in figure 2.

### 15   Example 2

Disposable test strips of the type described in PCT/AU96/00724 were modified by adhering a heater element to the base of the strip, beneath the sample receiving area. The heater element was fabricated by sputtering two parallel low resistance metallic tracks onto a polyester substrate and then sputtering a thin, resistive metallic track at right  
20   angles to the low resistance metallic tracks, such that the resistive metallic track contacted both of the parallel low resistance tracks. This heater was then glued to the base of the disposable test strip using an adhesive, such that the resistive track was positioned directly beneath and facing the sample receiving area on the strip.

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The parallel low resistance tracks protruded from the end of the strip and provided electrical contacts for a power supply to power the heater. The power supply for the heater consisted of a battery and a variable resistor, which could be adjusted to vary the rate of heating. Whole blood samples were introduced into the sample receiving area of the strip and 20 seconds allowed for the glucose present in the sample to react with the sensor reagents. Current was then collected for ten seconds and analyzed according to the methods described in PCT/AU96/00723. The results of these tests for blood samples with haematocrits of 65%, 46% and 20% and glucose concentrations between 2.8 mM and 32.5 mM are shown in figure 3.

Although the invention has been herein described with reference to electrochemical methods for measuring glucose concentration in blood it will be appreciated that the method may also be applied utilising suitable spectroscopic or other measuring methods and to samples other than blood and to analytes other than glucose.

## THE CLAIMS OF THE INVENTION ARE AS FOLLOWS:

1. A method for determining the concentration of an analyte in a sample comprising the steps of:  
heating the sample in a disposable test cell; and  
5 measuring the concentration of the analyte or the concentration of a species representative thereof in the sample at a predetermined point on a reaction profile by means that are substantially independent of temperature.
2. A method according to Claim 1 wherein the predetermined point on the reaction profile is a steady state.
- 10 3. A method according to Claim 1 or Claim 2 wherein the species representative of the concentration of the analyte is a mediator.
4. A method according to Claim 3 wherein the mediator is an enzyme mediator.
5. A method according to any one of the preceding claims wherein the sample is heated by an exothermic reaction produced upon contact of said sample with at  
15 least one suitable reagent.
6. A method according to Claim 5 wherein the at least one suitable reagent is a salt which liberates heat on dissolution.
7. A method according to Claim 6 wherein the salts are selected from the group consisting of aluminium chloride, lithium halides, lithium sulfate, magnesium  
20 halides, and magnesium sulfate.
8. A method according to Claim 5 wherein the at least one suitable reagent is a two component system which liberates heat upon mixing.

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9. A method according to Claim 8 wherein each of the two components are placed in separate locations in a sensor during fabrication.
10. A method according to Claim 9 wherein said two components are placed as coatings upon opposite internal cell walls of a sensor.
- 5 11. A method according to Claim 1 wherein the sample is heated electrically.
12. A method according to Claim 11 wherein said sample is heated by means of a current applied to resistive elements associated with said measuring means.
13. A method according to any one of the preceding Claims wherein the concentration of the analyte is measured by an electrochemical measurement.
- 10 14. A method according to Claim 13 wherein the sample is heated prior to and/or during conduct of the electrochemical measurement.
15. A method according to any one of the preceding Claims wherein the sample temperature is raised by from 5 to 15°C.
16. A method according to any one of the preceding Claims wherein the sample temperature is raised within a period of 2-10 seconds.
- 15 17. A method according to any one of the preceding Claims wherein a peak temperature is reached within 2-5 seconds.
18. A method according to any one of the preceding Claims wherein the analyte is glucose.
- 20 19. A method according to any one of the preceding Claims wherein the sample is blood.
20. A method according to Claim 19 wherein the blood sample is combined with an enzyme.

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- 21 A method according to Claim 20 wherein the enzyme is glucose dehydrogenase (GDH) which oxidises glucose and is converted to reduced GDH.
22. A method according to Claim 21 wherein an oxidising mediator is present.
23. A method according to Claim 22 wherein said oxidising mediator is ferricyanide.
- 5 24. A method according to Claim 23 wherein said ferricyanide reacts with said produced GDH to produce ferrocyanide.
25. A method according to Claim 24 wherein the ferrocyanide produced is sensed to produce a signal representative of the glucose concentration of the sample.
26. A method according to Claim 25 wherein the sensing is by electrochemical  
10 means.
27. A method according to Claim 25 wherein the sensing is by a spectroscopic means.
28. An electrochemical cell comprising a spacer pierced by an aperture which defines a cell wall, a first metal electrode on one side of the spacer extending  
15 over one side of the aperture, a second metal electrode on the other side of the spacer extending over the side of the aperture opposite the first electrode, means for admitting a sample to the cell volume defined between the electrodes and the cell wall, and means for heating a sample contained within the cell.
29. An electrochemical cell according to Claim 28 wherein the means for heating a  
20 sample is an electrically resistive element.
30. A method of heating an electrochemical cell as defined in Claim 28 including the step of applying a potential across the resistive element to regenerate the required amount of heat, interrupting the potential across the resistive element

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and applying a potential between the first electrode and second electrode to perform the electrochemical assay of the analyte.

31. A method according to Claim 30 wherein a potential across the resistive element is maintained during the assay of the analyte at an initial level or at a lower level sufficient to substantially maintain the sample temperature of the desired level.
32. A method according to Claim 30 or 31 wherein means for applying potential to the resistive element is such that the current flowing through the resistive element is monitored and the potential automatically adjusted so as to maintain the required power output.
33. A method according to Claim 32 wherein the power output can be adjusted on the basis of ambient temperature measured by a separate sensor.
34. A method of determining the concentration of an analyte in a sample substantially as herein described with reference to any one of the examples.
35. An electrochemical cell substantially as herein described with reference to figure 1 or any one of the examples.
36. A method of heating an electrochemical cell substantially as herein described with reference to any one of the examples.

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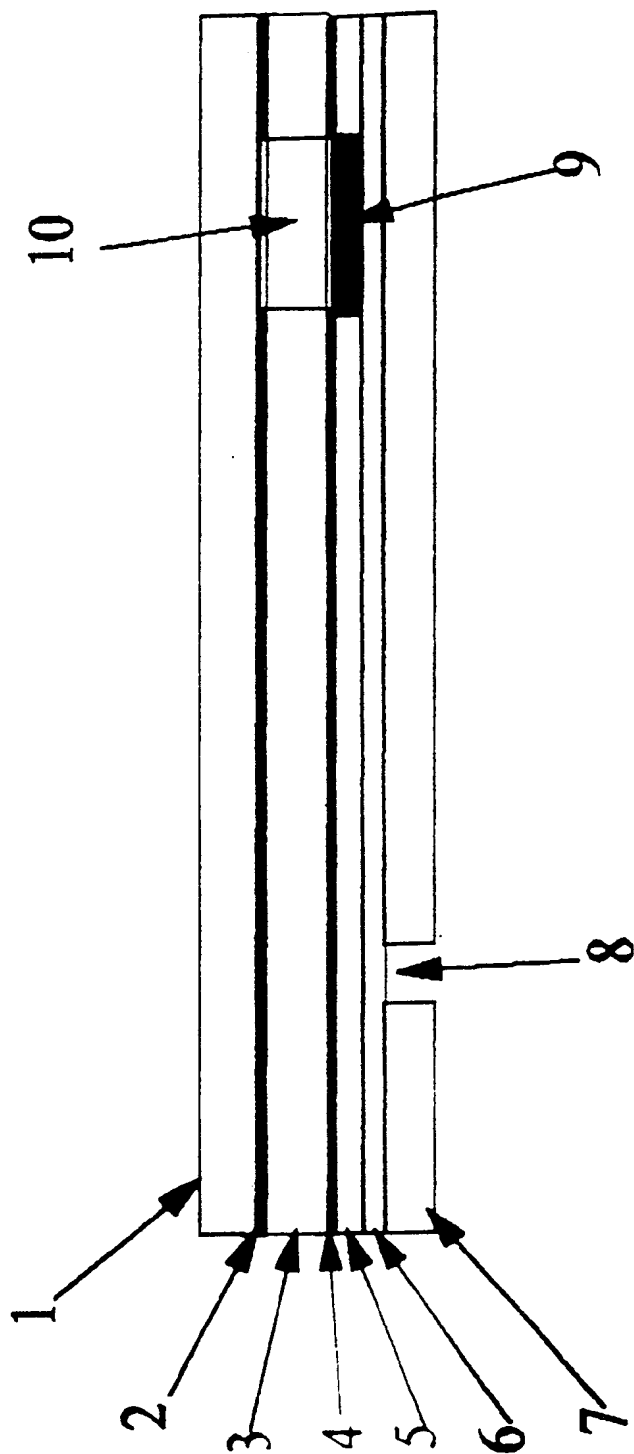


FIGURE 1



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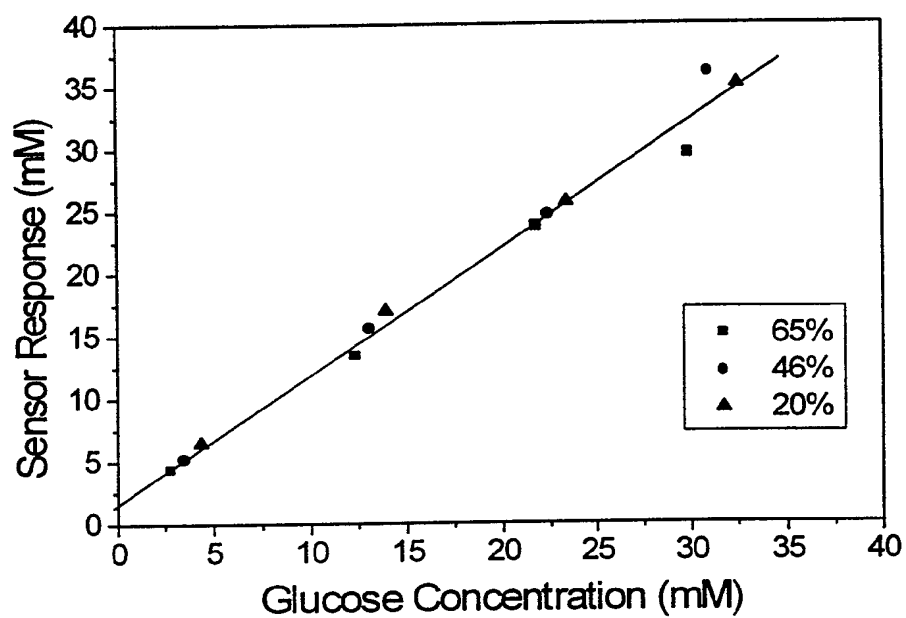


Figure 2

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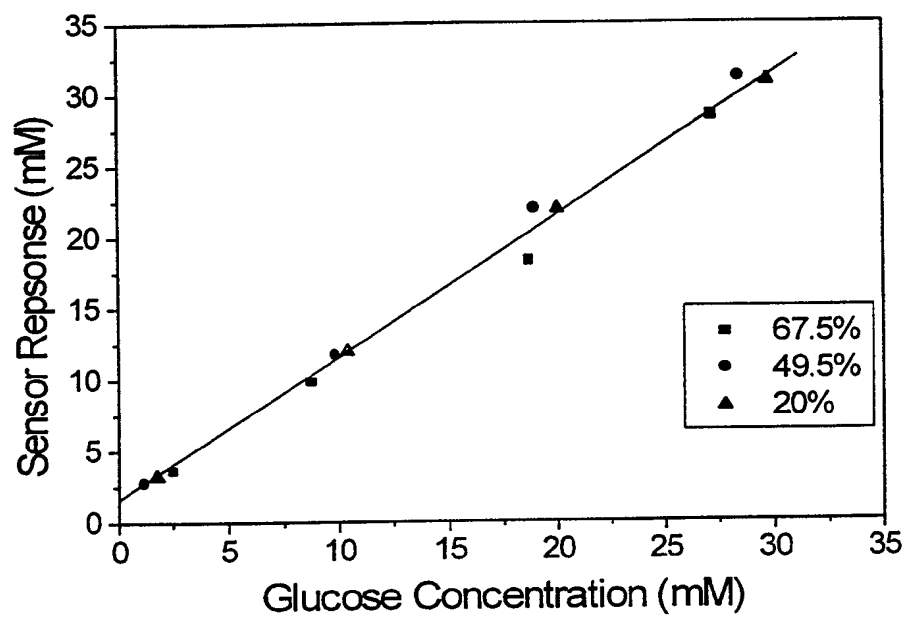


Figure 3

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/AU 99/00152

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
Int Cl <sup>6</sup> : G01N 27/26, 27/403		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols) IPC6 G01N 27/-, 33/48, 33/49, 33/50; C12Q 1/54, 1/66		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched AU:IPC as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) WPAT, keywords		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5607565 A (AZARNIA et al) 4 March 1997 Whole document	1-27, 34
Y	Whole document	28, 29, 35
Y	WO 97/18464 A (MEMTEC AMERICA CORPORATION) 22 May 1997 Whole document	28, 29, 35
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex		
<p>* Special categories of cited documents:</p> <p>"A" Document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" Earlier application or patent but published on or after the international filing date</p> <p>"L" Document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" Document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" Document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>		
Date of the actual completion of the international search 19 April 1999		Date of mailing of the international search report 23 APR 1999
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200 WODEN ACT 2606 AUSTRALIA Facsimile No.: (02) 6285 3929		Authorized officer  M.J. O'ROURKE Telephone No.: (02) 6283 2017

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 99/00152

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Patent Abstracts of Japan JP, 08-062179 A (HITACHI LTD HITACHI INSTR ENG CO LTD) 8 March 1996 Whole document	1-36
A	US 5512159 A (YOSHIOKA et al) 30 April 1996 Whole document	1-36

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/AU 99/00152

## Box 1 Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please refer to supplemental box

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.  
PCT/ AU 99/00152

### Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

The international application does not comply with the requirements of unity of invention because it does not relate to one invention or to a group of inventions so linked as to form a single general inventive concept. In coming to this conclusion the International Searching Authority has found that there are different inventions as follows:

1. Claims 1 to 27 and 34 are directed to a method of determining the concentration of an analyte in a sample including the steps of heating the analyte in a disposable test cell and measuring concentration by means which are substantially independent of temperature. It is considered that this combination of features comprises a first "special technical feature".
2. Claims 28, 29 and 35 relate to an electrochemical cell including a spacer pierced by an aperture, first and second electrodes, and means for admitting and heating a sample. It is considered that this combination of features comprises a second "special technical feature".
3. Claims 30 to 33 and 36 relate to a method of heating the cell of claim 28. It is considered that the method steps comprise a third "special technical feature".

Since the abovementioned groups of claims do not share any of the technical features identified, a "technical relationship" between the inventions, as defined in PCT rule 13.2 does not exist. Accordingly the international application does not relate to one invention or to a single inventive concept, a priori.

However since all these inventions share the same classification under the IPC they could be searched together without effort which would warrant an additional fee.

# INTERNATIONAL SEARCH REPORT

## Information on patent family members

International application No.  
**PCT/AU 99/00152**

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report				Patent Family Member			
US	5607565	EP	760946	WO	9630751		
US	5512159	CA	2068475	JP	5196595		
JP	08-062179						
WO	9718464	AU	75549/96	AU	75550/96	CN	1188545
		EP	882226	WO	9718465		

END OF ANNEX